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Filed : **April 9, 2004**

SUMMARY OF INTERVIEW

The following is a summary of the telephone interview held on January 19, 2005 among Applicant Elliott C. Lasser, M.D., Applicant's representative Marc Morley and Patent Office representatives, Examiner Sharareh and Supervisor Padmanabhan. Applicant first wishes to thank Examiner Sharareh and Supervisor Padmanabhan for accommodating the interview and for their helpful comments during the interview

Exhibits and/or Demonstrations

No exhibits or demonstrations were presented during the interview.

Identification of Claims Discussed

Claims 1-21 were discussed during the interview.

Identification of Prior Art Discussed

The cited art of record in the Office Action dated January 7, 2005 was discussed during the interview.

Proposed Amendments

The parties discussed the cancellation of Claims 1-17, the amendment of Claims 18 and 20, and the addition of new dependent claims.

Principal Arguments and Other Matters

The parties discussed the distinctions between Claims 18 and 20 and the cited art, and discussed the amendments those claims.

Results of Interview

Not applicable (N/A).

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REMARKS

Claims 1-17 are cancelled without prejudice toward future prosecution. Claims 18 and 20 have been amended as set forth above. The specific changes to the claims are shown above with insertions shown in underlined text and ~~deletions shown in strikethrough text~~. Also, entry of new Claims 22-23 is requested. As evidenced below, the amendments and the new claims do not introduce new matter into the application. Upon entry of the above-mentioned amendments, Claims 18-23 are pending.

Support for Amendments

As discussed during the interview, the preamble of Claims 18 and 20 has been broadened to recite "treating." As set forth in the Office Action, the specification is "enabling for treating or prophylactically treating allergic conjunctivitis or allergic rhinitis." Claims 18 and 20 have thus been amended to broadly cover "treating," including prophylactic treatment. The amendment is supported by the application as filed, particularly by Examples 5 and 6. Also, as discussed during the interview, Claims 18 and 20 have been amended to recite that the X-ray contrast media is "selected from triiodinated, completely or partially substituted, benzene moieties existing in the form of a dimer," which is supported by the specification as filed, in particular, original Claim 12. Support for the amendment to Claim 20 to delete "by drop installation" is found in the specification at paragraph [0049] which states that IODIXANOL was delivered into both nostrils. No other amendments have been made.

Provisional Election

The Office Action states that a provisional election with traverse was made in which a species election was made. Applicant clarifies that the elected species is contrast agents such as "IODIXANOL," not "IOTROLAN."

Discussion of Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 1-21 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. According to the Office Action, the specification is "enabling for treating or prophylactically treating allergic conjunctivitis or allergic rhinitis," but "does not reasonably provide enablement for treating or preventing all types of allergic reactions including drug allergies, food allergies,

etc." The Office Action further asserts that the specification does not adequately enable methods of preventing allergic reactions in any susceptible subjects, nor does it provide adequate enablement for using any type of X-ray contrast media that could provide the intended benefits.

Independent Claims 18 and 20 have been amended as set forth above, consistent with the discussion during the interview. Claim 18 recites a method of treating allergic conjunctivitis, and Claim 20 recites a method of treating allergic rhinitis. As acknowledged in the Office Action, the specification is enabling for treating or prophylactically treating allergic conjunctivitis or allergic rhinitis. Furthermore, Claims 18 and 20 have been amended to recite that the X-ray contrast media is "selected from triiodinated, completely or partially substituted, benzene moieties existing in the form of a dimmer." The specification teaches how to make or obtain such contrast media, as well as how to use such media in the claimed methods. *See* Examples 5-6.

Therefore, reconsideration and withdrawal of the instant enablement rejection is respectfully requested.

Discussion of Rejection under 35 U.S.C. § 102 - Anticipation

Claims 1 and 8-17 were rejected under 35 U.S.C. § 102(a) as being anticipated by Katayama et al. (Radiology 175:621-628 (1990)). Claims 1-17 have been cancelled without prejudice. Therefore, this rejection will not be further addressed.

Discussion of Rejection under 35 U.S.C. § 103 - Obviousness

Claims 1 and 7-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lasser et al. (Acad Radiol 5 (Suppl. 1): S95-S98 (1998)) in view of Roitt et al. (Mosby Co., Ltd. pages 19.1 and 19.7-19.10 (1985)). Again, Claims 1-17 are no longer pending. Therefore, the rejection of those claims under § 103(a) is not specifically discussed herein.

Claims 2-6 and 18-21 were rejected under § 103(a) as being unpatentable over Lasser et al. in view of Roitt et al., and further in view of Bhargava et al. (Drugs of today 34(11):957-971 (1998)) and MacLeod et al. (Clin Exp Allergy 27:1328-1334 (1997)). According to the Office Action, Lasser et al. concludes that contrast agents can cause antigen excess and lead to inhibition of cellular content, which mediates histamine release. Further, the Office Action states that Lasser et al. merely fails to explicitly show administration of a contrast agent for treatment of an allergic reaction. The Office Action states that Roitt et al is merely used to show that allergic

and hypersensitivity reactions are mediated by mast cell activation through antibody complex formation and the release of proinflammatory mediators The Office Action acknowledges that Lasser et al. and Roitt fail to describe the topical administration of contrast agents for treatment of allergic rhinitis or conjunctivitis, but asserts that Bhargava shows the use of compositions for the treatment of allergic rhinitis, and that MacLeod shows the use of compositions for treatment of allergic conjunctivitis. Applicant respectfully disagrees and submits that independent Claims 18 and 20 are not obvious in view of the combination of the four references.

A proper *prima facie* obviousness rejection requires, *inter alia*, consideration of "whether the prior art would have suggested to those of ordinary skill in the art that they should ... carry out the claimed process, and ... whether the prior art would also have revealed that in so ... carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

In this case, among other reasons, there is no *prima facie* case of obviousness because there is no reasonable expectation that combining the cited art references would successfully result in the claimed methods of treating allergic rhinitis and conjunctivitis.

Lasser et al. recognized that X-ray contrast media could cause adverse reactions when administered. *See* Lasser et al. at page S95. For example, Lasser et al. recognized that X-ray contrast media cause "anaphylactoid" reactions (*i.e.*, harmful reactions similar to anaphylaxis) such as seen when the body is exposed to some antigens. *See id.* Nevertheless, Lasser et al. noted that "no one has been able identify antibodies produced by the injection of contrast media in experimental animals" without binding the media to a protein before injection. *See id.* In view of this, Lasser et al. sought to further investigate the immunologic properties of X-ray contrast media, specifically, to determine if the media function as antigens in causing the severe adverse physiological reactions. *See id.*

In order to the immunology of the X-ray contrast media, Lasser et al. performed passive hemagglutination inhibition assays. *See id.* The assays sought to determine if the various X-ray contrast media would compete with the two studied antigens, Ovalbumin and γ-globulin, for their antibodies. *See* Lasser et al. at pages S95 and S96. Lasser et al. also performed LD_{100} studies with rats injected with X-ray contrast media to study the toxicity of several contrast media and combinations of the various contrast media. *See* Lasser et al. at page S96.

Lasser et al. determined that all of the various X-ray contrast media competed, to some degree, with the two antigens (ovalbumin and γ-globulin) for the antibodies specific for the two antigens. *See id.* Thus, Lasser et al. concluded that the tested X-ray contrast media were able to compete with the two antigens for antibody binding. *See id.* Lasser et al. further concluded that the data indicate that the X-ray contrast media "have the potential to function as nonspecific pseudoantigens." *See id.*

Lasser et al. did not investigate whether the X-ray contrast media could be used to treat allergies or even to mediate the underlying causes of allergies. There is no discussion in Lasser et al. regarding the use of X-ray contrast media to treat or mediate allergy.

Contrary to assertions in the Office Action, Lasser et al. did not conclude that the X-ray contrast media can cause antigen excess and lead to inhibition of cellular content, which mediates histamine release. Lasser et al. noted a paradoxical situation, namely, that the more potent pseudoantigen contrast materials were the generally less toxic contrast media. *See* Lasser et al. at page S97. Lasser et al. stated that an explanation for this was "still to be reconciled." *See id.* However, Lasser et al. theorized that the greater antigenicity of the less toxic molecules might be due to the concept of "antigen excess." *See id.* Lasser et al. theorized that rather than cause the adverse anaphylactoid reactions, when excess contrast media were present, the contrast media "might" act in a protective fashion. *See id.*

Thus, Lasser et al. did not disclose the use of X-ray contrast media or teachings that would indicate the possible use of X-ray contrast media to treat allergic reactions of any kind. Lasser et al. provided no data or disclosure showing that the X-ray contrast media could prevent allergy or mediate the underlying mechanisms leading to allergy. At most Lasser et al. theorized that the concept of "antigen excess" might provide an explanation for why some contrast media with less toxicity are better at competing for antibodies against the specific antigens. Again, Lasser et al. did not show or conclude that X-ray contrast media lead to inhibition of cellular content, which mediates histamine release.

Thus, the Lasser et al. reference is an improper reference upon which to base an obviousness rejection because it does not disclose the use of X-ray contrast mediate to treat, regulate or mediate allergic reactions. Lasser et al. notes that additional investigation is necessary to understand the immunologic effects of the contrast media. Therefore, one of ordinary skill in the art would not reasonably expect that combining Lasser et al. with the other

respective references would successfully result in the claimed methods of treating the respective eye and nose allergies.

Furthermore, X-ray contrast media are normally used systemically not topically. The X-ray contrast media described in Lasser et al. when traditionally used to take X-rays are injected into the patient. The toxicity studies done in Lasser et al. were done by injecting the contrast media into laboratory rats. Lasser et al. did not disclose topical administration of X-ray contrast media, and in particular, topical administration into the nose or eye. In fact, there would be no *a priori* way of knowing whether topical administration would result in alleviation or worsening of an eye or nose allergy. In view of this, one of ordinary skill in the art would not reasonably expect to successfully combine Lasser et al., which injected the contrast media into rats, with the secondary references for topical use in the nose and eyes There is no reasonable expectation of success for the combination of references.

Also, it is worth noting that it is generally accepted that biological systems are unpredictable. Untested theories, such as the theory put forth by Lasser et al. regarding antigen excess, fail to meet the standard for predictability or reasonable expectation of success. One of ordinary skill in the art would not reasonably expect that the combination of references would successfully result in the claimed methods because of the lack of predictability and the speculative nature of the statements in Lasser et al.

Because of the unlikelihood of success and the deficient teaching in Lasser et al., only with the benefit of hindsight, using the instant application and claims as a roadmap, could the Patent Office have assembled the combination of cited references.

Therefore, the claimed methods of treating allergic conjunctivitis and allergic rhinitis are not obvious in view of the three combined references because there is no likelihood of success. For all of the above reasons, Applicant respectfully requests withdrawal of all rejections under 35 U.S.C. § 103, and allowance of the pending application.

Conclusion

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any

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remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3/14/05

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